Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 71, 74-76, and 79-111 are pending in the application, with claim 71 being the independent claim. Claims 72, 73, 77, and 78 have been cancelled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to pursue the canceled subject matter in a co-pending application. Claims 71 and 74-76 have been amended and claims 79-111 have been added.

This Amendment is being filed along with a request for continued examination. Therefore, entry of the new and amended claims is respectfully requested.

Support for the amendment of claims 71 and 74-76 can be found in the present specification at page 2, lines 20-24, and page 4, lines 25-27 (9 or 10 amino acids); page 2, lines 22-26 and page 4, lines 23-27 (recited motifs); and page 5, lines 1-11 and page 30, lines 1 and 17 (HPV (human papilloma virus), Plasmodium falciparum (malaria), and the other recited antigens).

Additionally, support for the HLA molecules encoded by the "B0701, B3501, B3502, B3503, B5101, B5301, B5401, and CW0601 alleles" of claim 71 is found in the present specification, which states:

> For assays of peptide-HLA interactions (e.g., quantitative binding assays) cells with defined MHC molecules are useful. A large number of cells with defined MHC molecules, particularly MHC class I molecules, are known and readily available. . . . *Table 3 lists some B cell lines suitable for use as sources for HLA-B and HLA-C alleles*, which are particularly *useful in the present invention.*

(Specification at page 9, lines 1-3 and 12-13 (emphasis added).) Further, Table 3 on page 10 lists each of the HLA alleles recited in claim 71.

For the Examiner's convenience, Applicants have attached a Table setting forth examples of support in this and two priority applications for the amended and added claims.

The specification has been amended to correct typographical errors and to claim priority directly to two of the previously specified, pending, priority applications. The amendment of priority does not change the earliest priority application being claimed. Therefore, no petition is required.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and further request that they be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph - New Matter

The rejection of claims 71, 72 and 74-77 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that "was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed subject matter" was maintained. (Paper 39 at 3.) The Office Action took the position that 8-mers and 11-mers were not supported; binding of 8-mers and 11-mers to at least two, at least three, or more than three HLA molecules was not supported; and IC_{50} values for certain peptide lengths was not supported. (*Id.* at 4-5.) Applicants respectfully traverse.

Claims 72 and 77 claims have been cancelled. Therefore, the rejection is moot as applied to these claims.

With respect to claims 71 and 74-76, and new claims 79-111, although Applicants believe the limitation 8-11 amino acids in length is fully supported in the present application and the priority applications, claim 71 has been amended to recite "9 or 10" amino acids in length, solely to expedite prosecution. Additionally, claim 76 no longer recites "8-11" amino acids in length. Further, the claims no longer recite an IC_{50} value. Applicants reserve the right to pursue the canceled subject matter in one or more co-pending applications. Support for the claim amendments is described in the preceding section.

As amended, the claims do not recite the language that the Examiner found objectionable.

The Office Action also stated that an "HPV" antigen and a "malarial" antigen in claim 77 are not supported. Claim 77 has been canceled. Claim 71 now recites an "HPV" antigen and a "Plasmodium falciparum" (malarial) antigen. As noted in the preceding section, support for these terms is found in the specification at page 5, lines 1-11 and page 30, lines 1 and 17.

Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph - Enablement

The rejection of claims 71, 72, and 74-76 as allegedly being nonenabled was maintained. (Paper 39 at 5.) The Office Action stated that there is a "high level of unpredictability" that a longer sequence would have HLA binding activity or that a sequence would bind an HLA molecule at an IC_{50} value less than 500nM. (*Id.* at 5-6.) Applicants respectfully traverse.

Applicants have cancelled claim 72 and have amended claim 71 such that it does not recite the phrase "IC_{50} less than 500 nM." The rejection is therefore moot with respect to this claim language.

With respect to claims 71, 74-76, and new claims 79-111, Applicants assert that the Office Action failed to establish a prima facie case of nonenablement.

The Office Action focused on "predictability" of binding. However, Applicants note that although the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, in *In re Angstadt*, the Court of Customs and Patent Appeals specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue. 537 F.2d 498, 503 (CCPA 1976). In *In re Angstadt*, the court disagreed with the proposition that, to be enabling, a disclosure must provide guidance such that one of ordinary skill in the art has a "reasonable certainty" of the outcome *before* performing an experiment. *Id.* The court stated:

> [if this proposition were true,] then ***all*** "experimentation" is "undue," since the term "experimentation" implies that the success of the particular activity is ***uncertain***. Such a proposition is contrary to the basic policy of the Patent Act.

Id.; see also id. at 504 ("In this art the performance of trial runs using different catalysts is 'reasonable,' even if the end result is uncertain, and we see no reason . . . why appellants should not be able to claim as their invention the broad range of processes which they have discovered.") As Judge Rich explained in *In re Vaeck*, 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to determine, without undue experimentation,

which species among all those encompassed by the claimed genus possess the disclosed utility."

Additionally, the Board of Patent Appeals and Interferences has repeatedly held that no single *Wands* factor – including unpredictability – is by itself dispositive of enablement. *Ex parte Springer,* Appeal No. 2000-0136 at 9 (BPAI, Jan. 9, 2002) (unpublished) ("[T]he examiner's case is premised on an incorrect legal standard. The examiner's conclusion of nonenablement seems to rest almost exclusively on an asserted lack of predictability in the art"). As the Board in *Ex parte Springer* recently stated:

> We emphasize again that unpredictability is not dispositive of enablement. Even a high degree of unpredictability can be offset by the other *Wands* factors.

Id. at 12; *see also Ex parte Mark*, 12 U.S.P.Q.2d 1905, 1907 (BPAI 1989) (unpublished) ("One skilled in the art is clearly enabled to ***perform such work as needed*** to determine ***whether*** the cysteine residues of a given protein are needed for retention of biological activity." (emphasis added)).

Here, as in *Ex parte Springer*, the Office Action's conclusion was based on an incorrect legal standard, i.e., an enablement rejection based on alleged unpredictability in the art. Moreover, Applicants respectfully assert that the claims are fully enabled. Applicants' disclosure provides sufficient guidance for making and using the claimed invention. A specification's description of the manner of making and using the invention is presumptively accurate. *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971); MPEP 2164.04. Further, the Examiner bears the burden to establish a reasonable basis to question the scope of enablement provided by a presumptively accurate disclosure. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993); MPEP 2164.04. In this case, the burden has not been met.

Although a prima facie case of nonenablement has not been established, Applicants nevertheless present the following comments to address the concerns expressed in the Office Action.

The claims are directed to nucleic acids encoding at least a first peptide, wherein the first encoded peptide binds at least two of the specified HLA molecules. Applicants respectfully submit that it would involve only routine experimentation to determine which nucleic acids fall within the scope of the claims. With respect to the length of the encoded peptide, it was known by 1994 that the presence of additional amino acids flanking an epitope prevents HLA binding. However, these epitopes are typically processed from larger proteins by intracellular proteosomes that recognize cleavage sites adjacent to the epitope, thus allowing binding of the processed epitope to HLA. Del Val et al., *Cell* 66:1145-1153 (1991); Eisenlohr et al., *J.Exp.Med.* 175:481-487 (1992). Thus, although longer peptides may not bind HLA, Applicants emphasize that the claims do *not* require the *longer* encoded peptides to bind, the claims only require the "first encoded" 9- or 10-mer to bind.

As to the question of whether a "first encoded" 9- or 10-mer would be processed from a longer peptide, several publications describe experiments showing that epitopes can be correctly processed from longer recombinant proteins such as chimeric proteins.

For example, Del Val et al. produced chimeric proteins containing a known epitope at different positions within an unrelated protein. Del Val et al., abstract. They found that although the yield of processed epitope differed depending on the positioning of the epitope within the chimera; nonetheless, the chimeras *were* correctly processed to produce the epitope. *Id.*, abstract and 1149, col. 2, 3d full paragraph. In addition, Del Val et al. showed that epitope yield from the inefficiently processed chimera was enhanced when oligo-alanine

sequences were inserted on either side of the epitope. *Id.*, abstract and 1147. col. 2 to 1148, col. 1. The present specification also describes the use of poly-Ala flanking sequences to improve MHC presentation, at page 24, lines 18-20.

Eisenlohr et al. also showed that flanking residues influence epitope processing. Eisenlohr et al., abstract. They also showed that the "the effect of negatively acting flanking sequences can be overcome by additional flanking sequences." *Id.*, 485, col. 2, 3d paragraph. The present specification also describes the use of naturally-occurring flanking sequences to improve MHC presentation, at page 24, lines 18-20. The results of Del Val et al. and Eisenlohr et al. were reviewed in Yewdell and Benninck, *Adv. Immunology* 52:1-123 (1992). Yewdell and Benninck summarized other studies in which epitopes were placed in recombinant proteins and were able to be processed no matter where they were located. Yewdell and Benninck at 31-32.

Thus, Yewdell and Benninck, Del Val et al., and Eisenlohr et al. provide evidence that one of ordinary skill in the art was aware, prior to 1994, that flanking sequences influence epitope processing, and that the artisan understood the need to determine experimentally whether a given epitope was efficiently processed in the context of a longer protein. Further, these publications also provide evidence that methods were available for making this experimental determination. The specification describes similar methods at page 26, lines 11-30. Importantly, these publications also provide evidence that recombinant proteins containing epitopes were correctly processed to produce the insert epitopes. Therefore, although the Office Action did not address the issue of antigen processing, Applicants have herein provided evidence that, prior to 1994, artisans had been successful at making recombinant proteins from which epitopes were correctly processed.

Therefore, even assuming, arguendo, that the Office Action established a prima facie case of nonenablement, Applicants have rebutted this showing by providing sufficient evidence that one skilled in the art would be able to make and use the claimed invention using the specification or the prior art as a guide.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, are respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 71 and 74-76 were rejected under 35 U.S.C. § 112, second paragraph, for reciting the term "discrete." (Paper 39 at 6.) Claim 72 was rejected for reciting the phrase "C-terminal amino acid." (*Id.*) Claim 71 was rejected for reciting the term "nm." (*Id.*) Claim 72 was rejected for reciting "[t]he nucleic acid molecule" "wherein the C-terminal amino acid is." (*Id.* at 7.) Claim 71 was rejected for reciting "an" nucleotide sequence. (*Id.*) Applicants respectfully traverse.

Applicants have canceled claim 72. Therefore, the rejection is moot as applied to that claim.

Claims 71 and 74-76 have been amended to no longer recite "discrete." In addition, claim 71 no longer recites "nm," and now recites "a" nucleotide sequence rather than "an" nucleotide sequence. Thus, the rejection is moot as applied to claims 71 and 74-76. Applicants therefore respectfully request reconsideration and withdrawal of the rejections.

The Effective Priority Date

The present application is entitled to the benefit of the filing date of at least Application No. 08/344,824, filed November 23, 1994, and Application No. 08/278,634, filed

July 21, 1994, one of which is co-pending with this application. The attached Table shows examples of support for the present claim language in these two priority applications.

Rejections Under 35 U.S.C. § 103

The rejection of claims 71, 72, and 74-77 under 35 U.S.C. § 103(a) over Sidney et al., *J. Immunology 157*:3480-90 (1996) in view of WO 93/03764 was maintained. (Paper 39 at 8.) The rejection of claims 71, 72, and 74-77 under 35 U.S.C. § 103(a) over Ramensee et al. *Immunogenetics 41*:178-228 (1995) in view of EP 0346022 A1 was also maintained. (*Id.* at 9.) Applicants respectfully traverse.

As discussed in the preceding section, the pending claims are entitled to the benefit of Application No. 08/278,634, filed July 21, 1994. Therefore, the publication of Sidney et al. is not available as prior art against the pending claims. In addition, WO 93/03764 does not teach or suggest a nucleic acid encoding a 9-10 amino acid long epitope comprising the motif recited in claim 71, or the nucleic acids recited in dependent claims 74-76 and 78-80. Therefore, WO 93/03764 does not render obvious the claimed invention.

Based on the effective filing of the pending claims, as discussed in the preceding section, Ramensee et al. is not available as prior art against the pending claims. Moreover, EP 0346022 A1 does not teach or suggest a nucleic acid encoding a 9-10 amino acid long epitope comprising the motif recited in claim 71, or the nucleic acids recited in dependent claims 74-76 and 78-80. Therefore, EP 0346022A1 does not render obvious the claimed invention.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and request that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Helene C. Carlson
Agent for Applicants
Registration No. 47,473

Date: 11/27/2002

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

Version with markings to show changes made

In the Specification:

The pending paragraph beginning at page 1, line 3, has been amended as follows:

This application is a continuation-in-part of U.S. Appl. ~~Serial~~ No. 08/753,615, filed November 27, 1996, abandoned, which is a continuation-in-part of U.S. Appl. ~~Serial~~ No. 08/590,298, filed January 23, 1996, abandoned, which is a continuation-in-part of U.S. Appl. ~~Serial~~ No. 08/452,843, filed May 30, 1995, which is a continuation-in-part of ~~application~~ U.S. Appl. ~~Serial~~ No. 08/344,824, filed November 23, 1994, which is a continuation-in-part of ~~application~~ U.S. Appl. ~~Serial~~ No. 08/278,634, filed July 21, 1994, abandoned; this application is also a continuation-in-part of said Appl. No. 08/344,824, filed November 23, 1994, and a continuation-in-part of said Appl. No. 08/452,843, filed May 30, 1995, all of which are incorporated herein by reference.

In the Claims:

Claims 72, 73, 77, and 78 have been canceled.

Claims 79-111 have been added.

Claims 71 and 74-76 have been amended as follows.

71. (Once amended) An isolated nucleic acid molecule comprising ~~an~~ a nucleotide sequence encoding at least a first ~~discrete~~ peptide consisting of ~~8-11~~ 9 to 10 amino acid residues wherein said first encoded peptide comprises a motif selected from the group consisting of: (a) a Pro residue at position 2 and a Leu residue at the C-terminal position; (b) a Pro residue at

position 2 and a Phe residue at the C-terminal position; (c) a Pro residue at position 2 and a Met residue at the C-terminal position; (d) a Pro residue at position 2 and a Trp residue at the C-terminal position; (e) a Pro residue at position 2 and an Ala residue at the C-terminal position; and (f) a Pro residue at position 2 and a Tyr residue at the C-terminal position; ~~the amino acid at position 2 of said peptide is proline and the C-terminal residue of said peptide is a hydrophobic amino acid residue and~~ wherein said first encoded peptide binds to at least two of the HLA molecules encoded by B0701, B1401, B3501, B3502, B3503, B5101, B5301, B5401 and ~~CW0602~~ CW0601 alleles; and wherein said first encoded peptide is from an HIV antigen, an HBV antigen, an HCV antigen, an HPV antigen, or a Plasmodium falciparum antigen ~~at IC_{50} values less than 500 nm~~.

74. (Once amended) The nucleic acid molecule of claim ~~72~~ 71, wherein said ~~discrete~~ first encoded peptide binds to at least three of said HLA molecules.

75. (Once amended) The nucleic acid molecule of claim 74, wherein said first encoded ~~discrete~~ peptide binds to more than three of said HLA molecules.

76. (Once amended) The nucleic acid molecule of claim 71, wherein said nucleotide sequence further encodes a second ~~discrete~~ peptide ~~consisting of 8-11 amino acids~~ which is a CTL epitope.

Table: Examples of Support

Claim Language	This Application	08/278,634	08/344,824
9 or 10	page 2, lines 23-26	page 2, lines 13-14 and 28-33; page 12, lines 7-10	page 2, lines 18-21; page 3, lines 3-5; page 13, lines 6-9
motifs	page 2, lines 23-26	page 2, lines 13-15	page 2, lines 18-21
bind to at least two or more, more than three HLA alleles	page 2, lines 26-27; page 3, line 28 to page 4, line 2	page 2, lines 16-17; page 3, lines 16-20	page 2, lines 21-22; page 3, lines 21-25
Antigens: HCV, HIV HPV, HBV	page 2, line 30 to page 3, line 2; page 5, lines 6-11; pages 28-29, table 5; pages 30-31, table 6; page 32, table 7	page 4, lines 18-22; page 41, lines 5-23; pages 43-47, table 11	page 4, lines 29-33; page 41, line 21 to page 42, line 3; page 41, lines 16-20
Alleles: B0701, B3501, B3502, B3503, B5101, B5301, B5401, CW0601	page 8, table 2; page 10, table 3;	page 7, table 2; page 9, table 3; page 33, table 6; page 37, table 8; page 38, table 9; page 39, table 10;	page 4, lines 29-33; page 8, table 2; page 10, table 3; page 33, table 6; page 37, table 8; page 38, table 9; page 39, table 10; page 41, line 21 to page 42, line 3; page 41, lines 16-20;
second CTL epitopes	page 22, lines 22-25	page 21, lines 16-19	page 22, lines 10-15
HTL epitope	page 25, lines 15-19		
leader (signal) sequence	page 24, lines 16-20		
endoplasmic reticulum retention signal	page 24, lines 16-20		
mRNA stabilization sequence	page 25, lines 6-7		